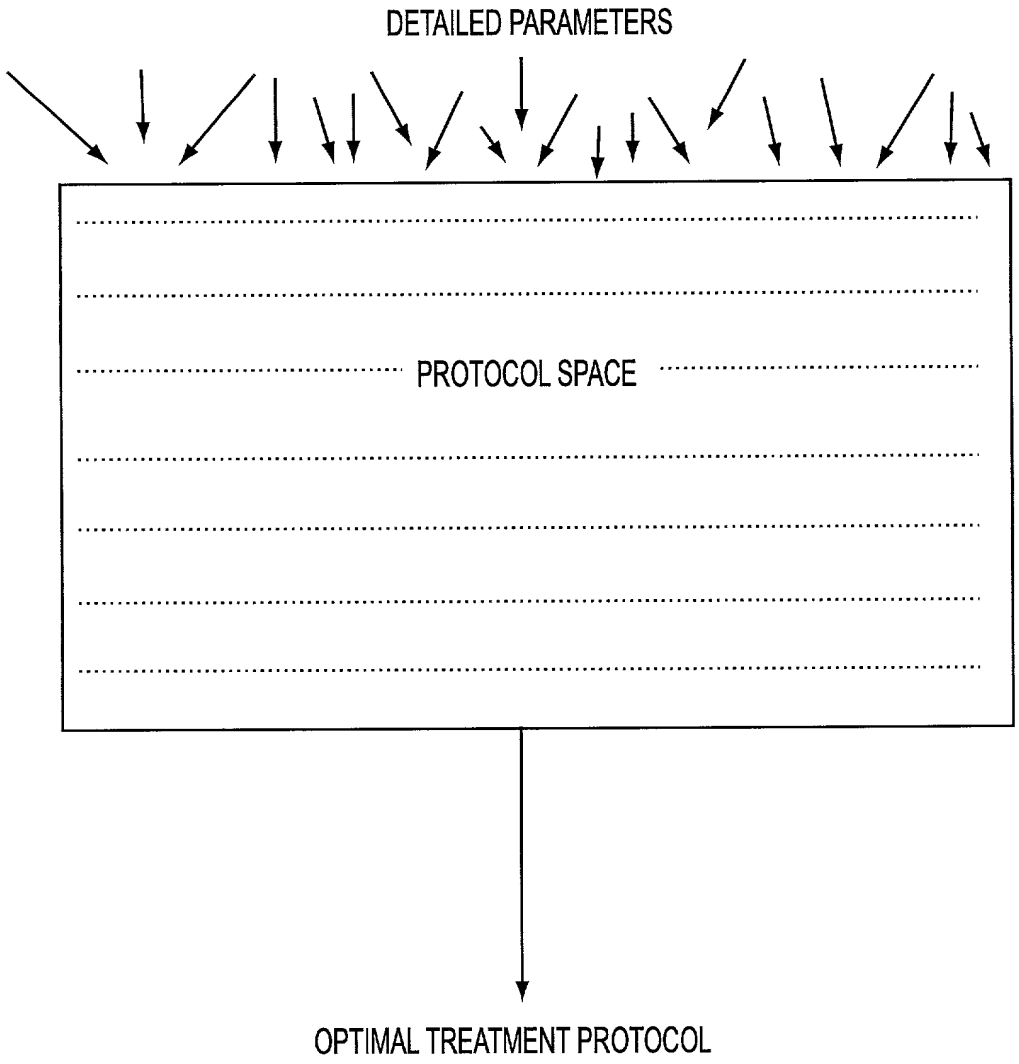
DETAILED PARAMETERS
PROTOCOL SPACE
OPTIMAL TREATMENT PROTOCOL

FIG. 1

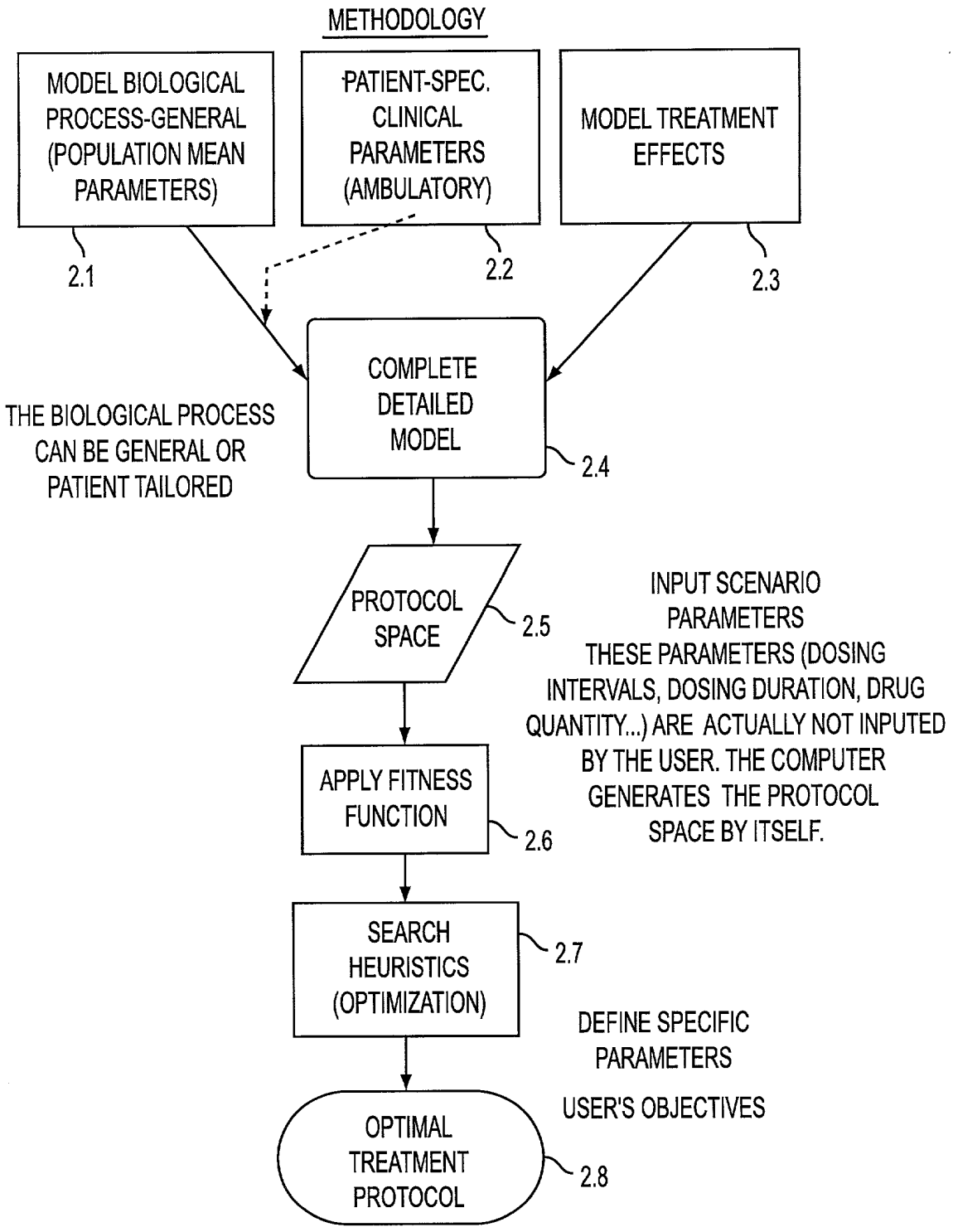
METHODOLOGY
MODEL BIOLOGICAL PROCESS-GENERAL (POPULATION MEAN PARAMETERS)
PATIENT-SPEC. CLINICAL PARAMETERS (AMBULATORY)
MODEL TREATMENT EFFECTS
2.1
2.2
2.3
COMPLETE DETAILED MODEL
2.4
THE BIOLOGICAL PROCESS CAN BE GENERAL OR PATIENT TAILORED
PROTOCOL SPACE
2.5
INPUT SCENARIO PARAMETERS
THESE PARAMETERS (DOSING INTERVALS, DOSING DURATION, DRUG QUANTITY...) ARE ACTUALLY NOT INPUTED BY THE USER. THE COMPUTER GENERATES THE PROTOCOL SPACE BY ITSELF.
APPLY FITNESS FUNCTION
2.6
SEARCH HEURISTICS (OPTIMIZATION)
2.7
DEFINE SPECIFIC PARAMETERS
USER'S OBJECTIVES
OPTIMAL TREATMENT PROTOCOL
2.8

FIG. 2A

METHODOLOGY (2)

ATTEMPTING TO OPTIMIZE SOME INSTANCE OF A CHEMOTHERAPY PROBLEM WITH A GIVEN SET OF SOLUTIONS...

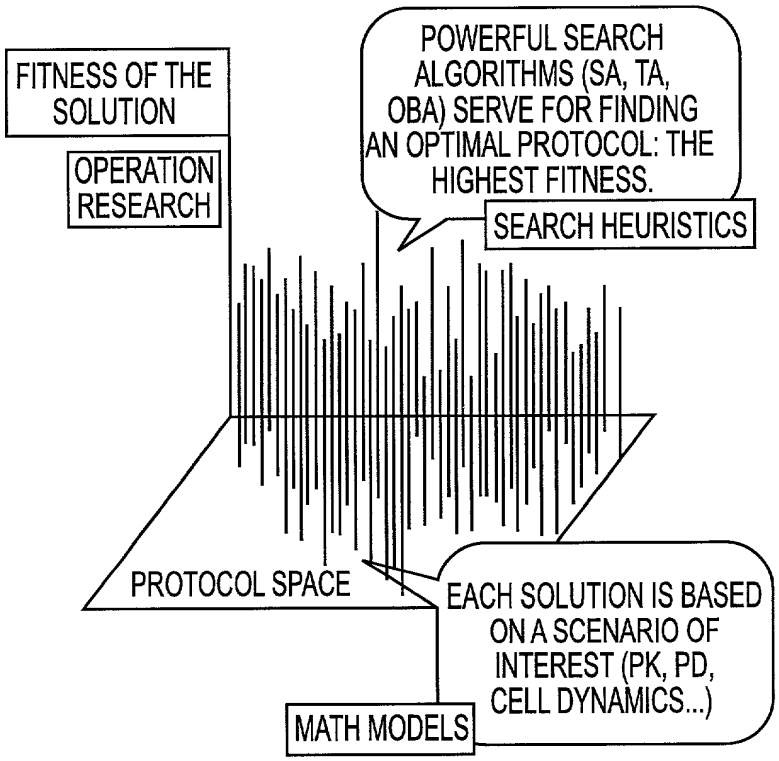

FIG. 2B

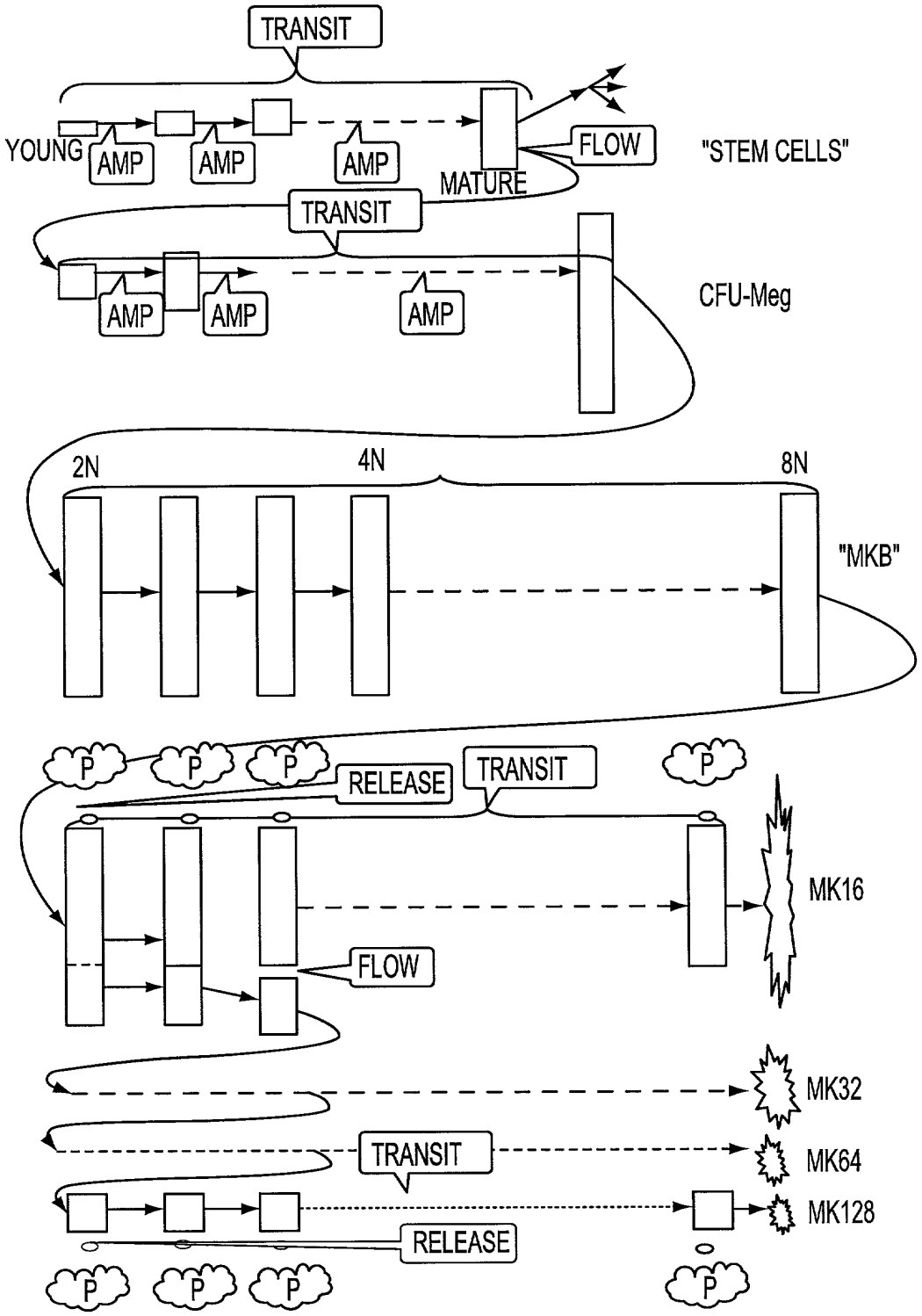
TRANSIT
YOUNG
AMP
AMP
AMP
MATURE
FLOW
"STEM CELLS"
TRANSIT
AMP
AMP
AMP
CFU-Meg
2N
4N
8N
"MKB"
P
P
P
RELEASE
TRANSIT
P
MK16
FLOW
MK32
TRANSIT
MK64
MK128
RELEASE
P
P
P
P

FIG. 3

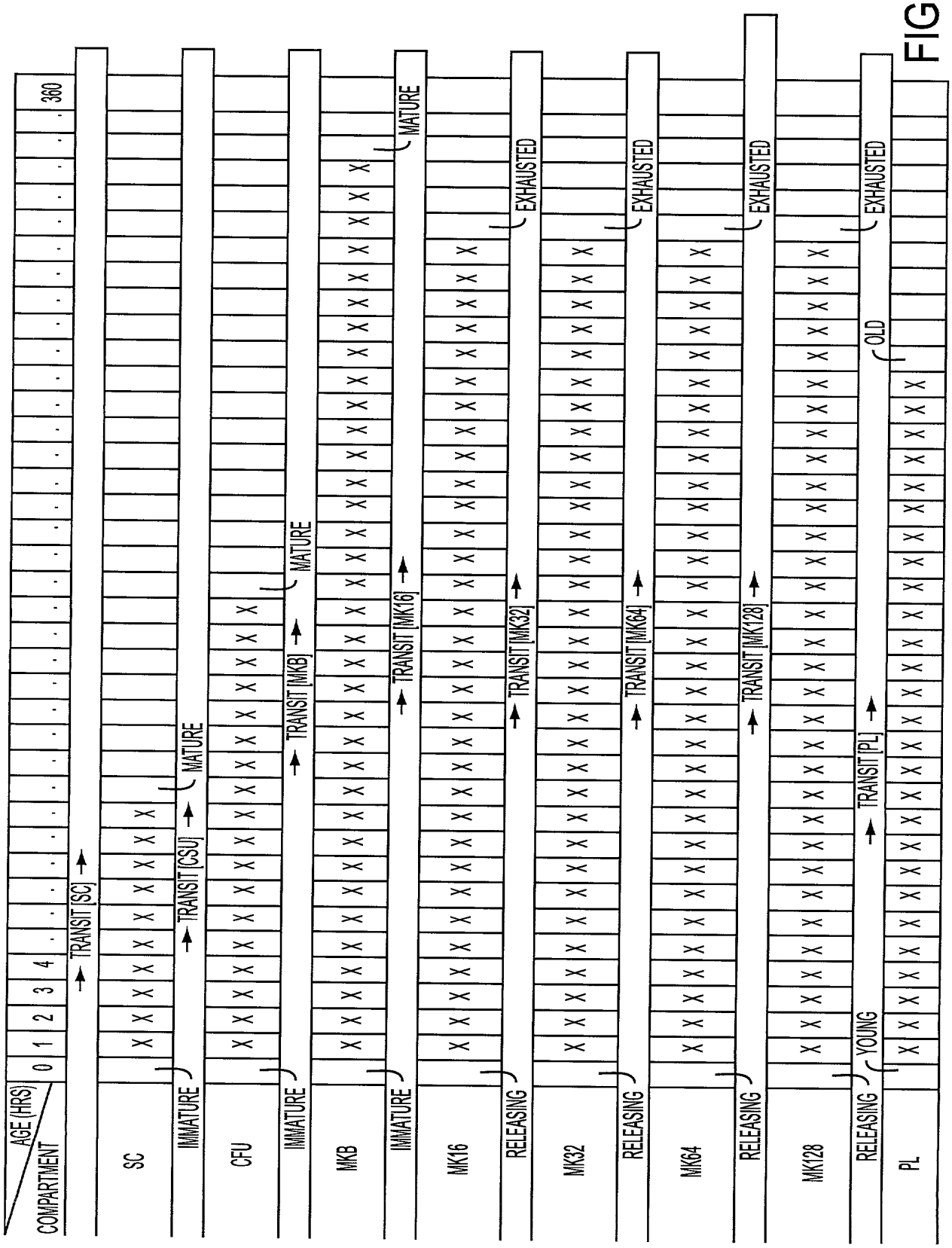
AGE (HRS)
COMPARTMENT
0
1
2
3
4
360
SC
CFU
MKB
MK16
MK32
MK64
MK128
PL
IMMATURE
MATURE
RELEASING
EXHAUSTED
YOUNG
OLD
TRANSIT [SC]
TRANSIT [CSU]
TRANSIT [MKB]
TRANSIT [MK16]
TRANSIT [MK32]
TRANSIT [MK64]
TRANSIT [MK128]
TRANSIT [PL]

FIG. 4

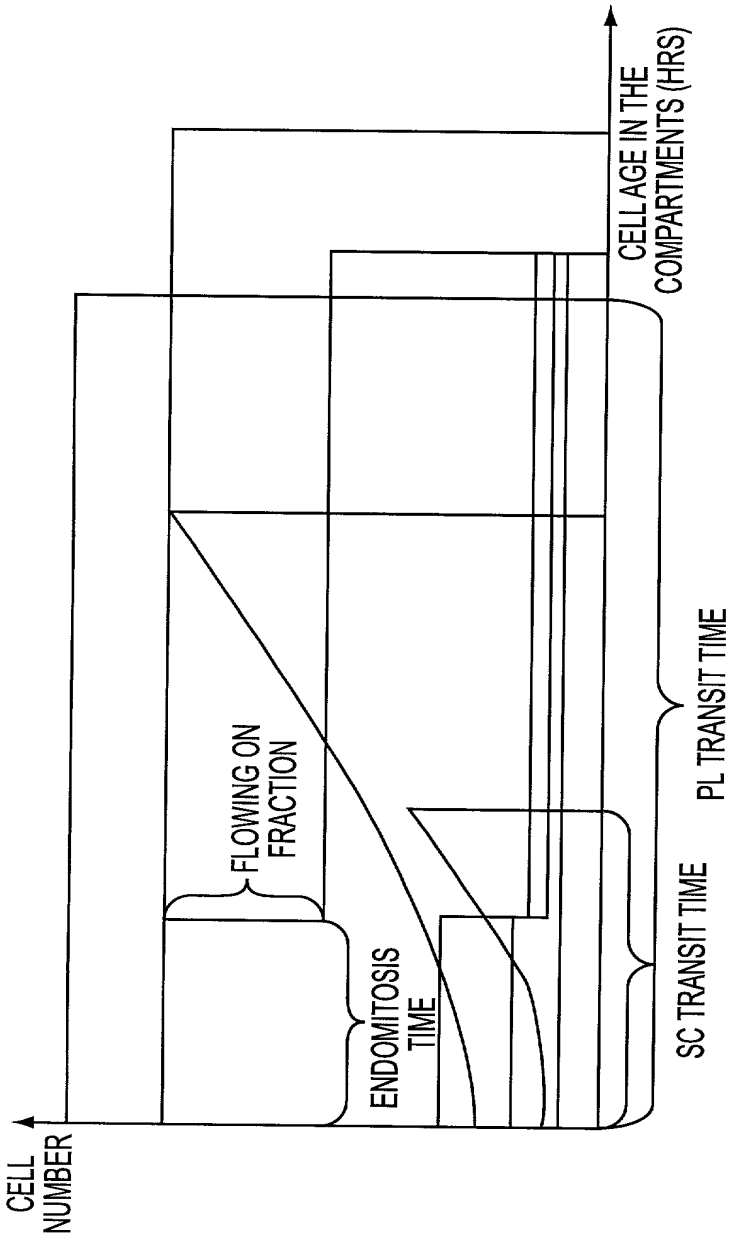
CELL AGE IN THE COMPARTMENTS (HRS)
CELL NUMBER
FLOWING ON FRACTION
ENDOMITOSIS TIME
SC TRANSIT TIME
PL TRANSIT TIME

FIG. 5

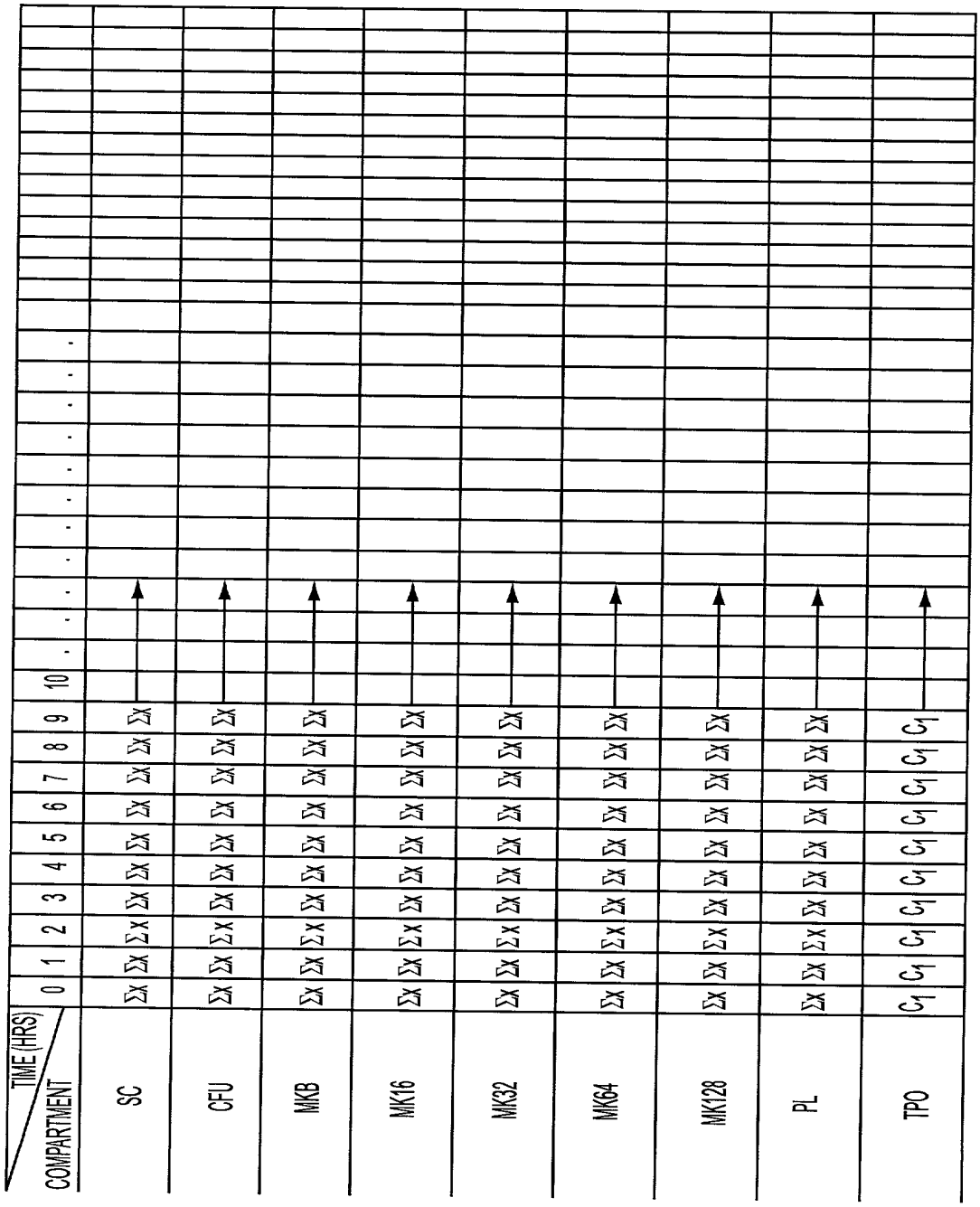
TIME (HRS)
COMPARTMENT
0
1
2
3
4
5
6
7
8
9
10
SC
GFU
MKB
MK16
MK32
MK64
MK128
PL
TPD

FIG. 6

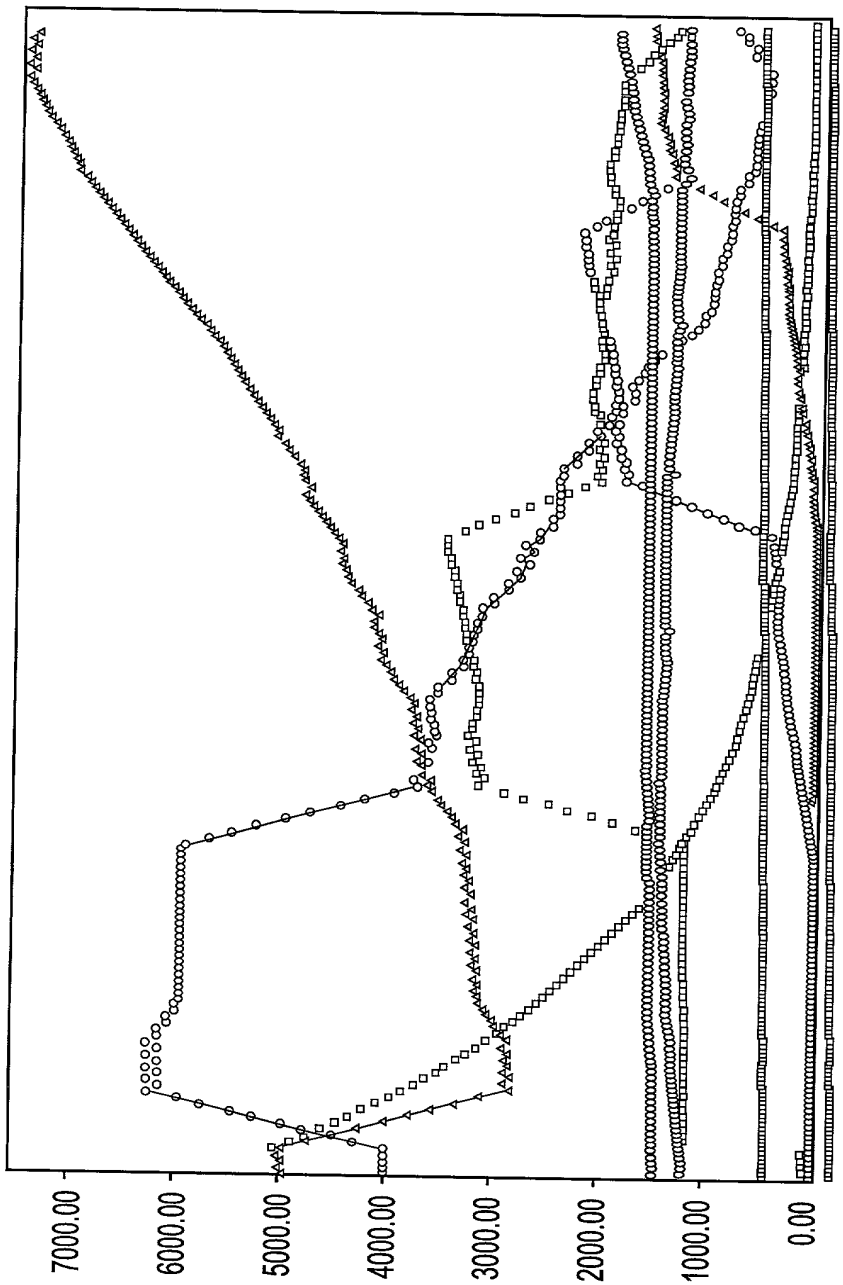

FIG. 7

SIMULATIONS SHOWING THAT IF THE PROTOCOL IS PRE-CALCULATED THEN A SIMILAR OR A HIGHER EFFICACY CAN BE OBTAINED USING 4-FOLD REDUCED TOTAL DOSE OF TPO.

TPO USE IN HEALTHY DONORS:

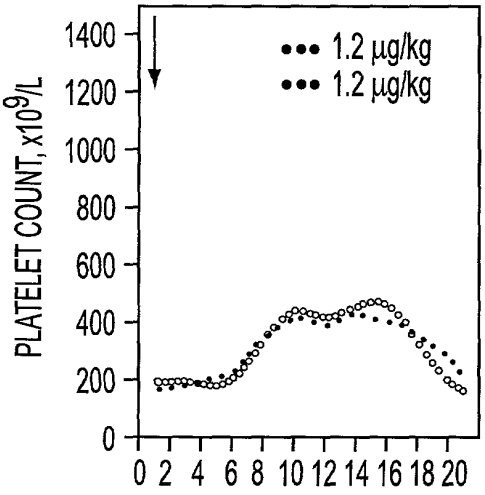

FIG. 8A

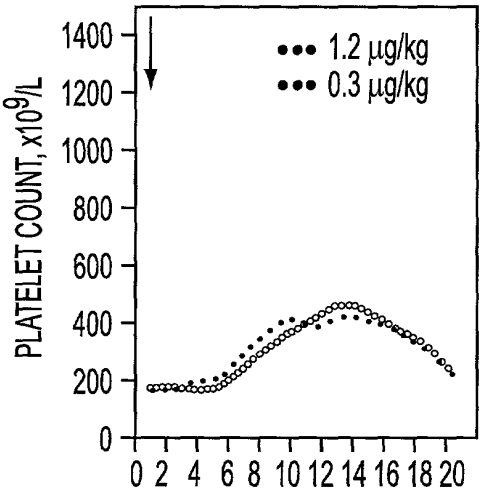

FIG. 8B

FIG. 8 TPO GIVEN TO HEALTHY DONORS- RESULTS OF TPO CLINICAL TRIALS FROM RECENT RESEARCH ON HEALTHY PLATELET DONORS, AS COMPARED TO OUR COMPUTER SIMULATION RESULTS. ARROWS INDICATE THE START OT TPO TREATMENT. (A) COMPARISON OF EXPERIMENTAL DATA FROM PUBLISHED ARTICLES[1] (BLACK) AND OUR MODEL SIMULATION (GREEN), IN BOTH TPO WAS GIVEN AS A SINGLE IV DOSE OF 1.2 µg/kg ON DAY 0. (B) COMPARISON OF THE SAME EXPERIMENTAL DATA (BLACK) AND OUR PROPOSED TPO ADMINISTRATION PROTOCOL; THE TOTAL DOSE IN THE SIMULATED PROTOCOL WAS 0.3 µg/kg (BLUE).

TPO USE IN PATIENTS RECEIVING CHEMOTHERAPY:

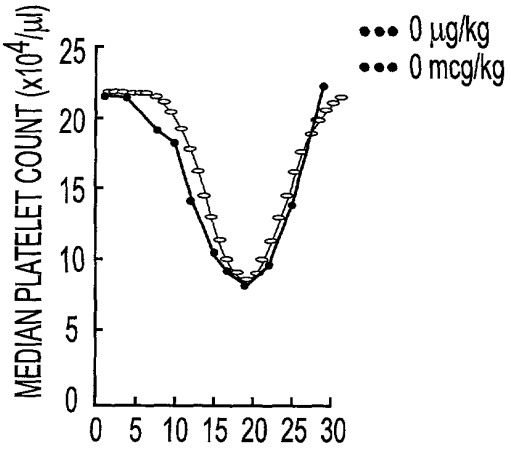

FIG. 9A

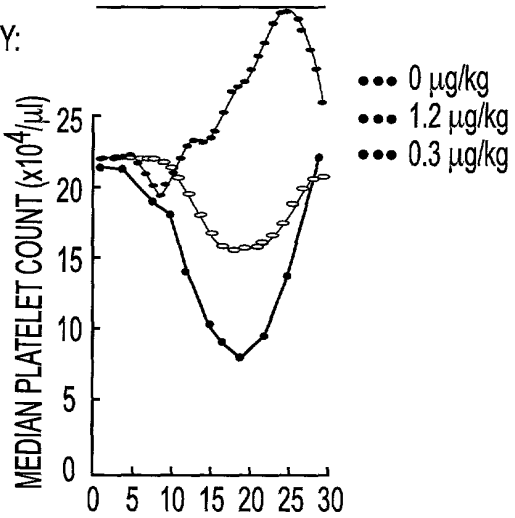

FIG. 9B

FIG. 9: TPO WITH CHEMOTHERAPY- (A) RESULTS OF CLINICAL TRIALS FROM RECENT RESEARCH ON THROMBOCYTOPENIA INDUCED IN PATIENTS RECEIVING SINGLE CARBOPLATIN CHEMOTHERAPY[2] DAY 0 (BLACK), AS COMPARED TO OUR MODEL SIMULATION OF THESE RESULTS (GREEN). (B) THE SAME EXPERIMENTAL DATA (BLACK); SIMULATIONS OF THE SAME EXPERIMENT, WITH ADDITION OF "CONVENTIONAL" TPO PROTOCOL OF A SINGLE IV DOSE OF 1.2 µg/kg ON DAY 0 (OLIVE); SIMULATIONS OF THE SAME EXPERIMENT UNDER OUR PROPOSED PROTOCOL THAT TOTALS 0.3 µg/kg (BLUE).

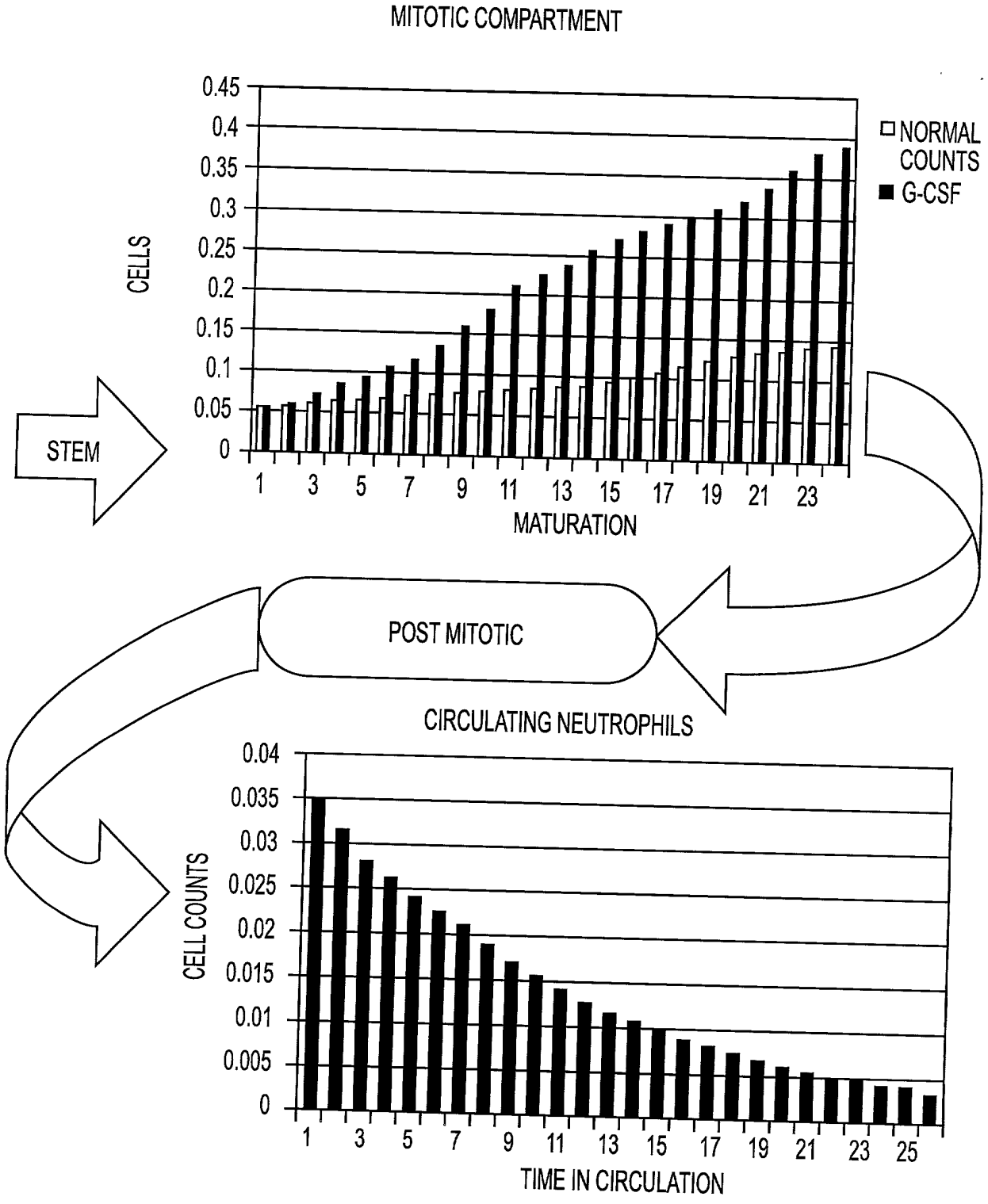
MITOTIC COMPARTMENT
CELLS
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
1 3 5 7 9 11 13 15 17 19 21 23
MATURATION
NORMAL COUNTS
G-CSF
STEM
POST MITOTIC
CIRCULATING NEUTROPHILS
CELL COUNTS
0.04
0.035
0.03
0.025
0.02
0.015
0.01
0.005
0
1 3 5 7 9 11 13 15 17 19 21 23 25
TIME IN CIRCULATION

FIG. 10

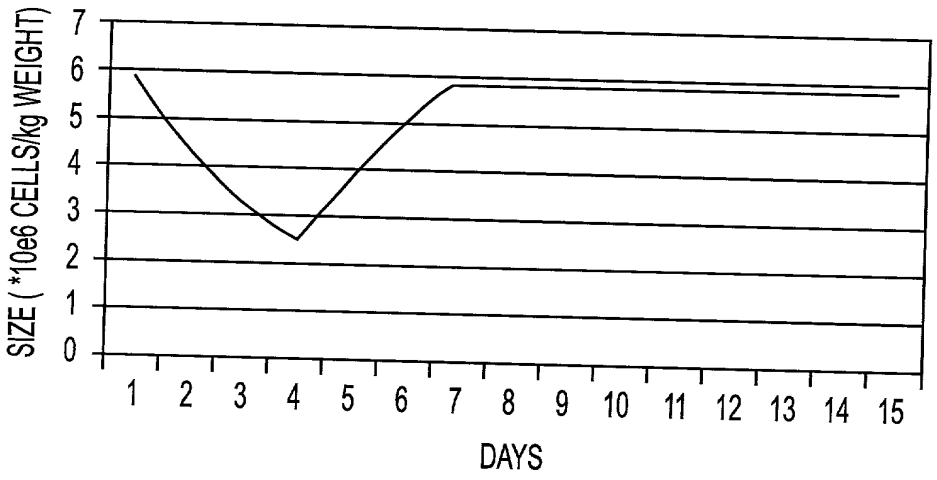
SIZE (*10e6 CELLS/kg WEIGHT)
0
1
2
3
4
5
6
7
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
DAYS

FIG. 11

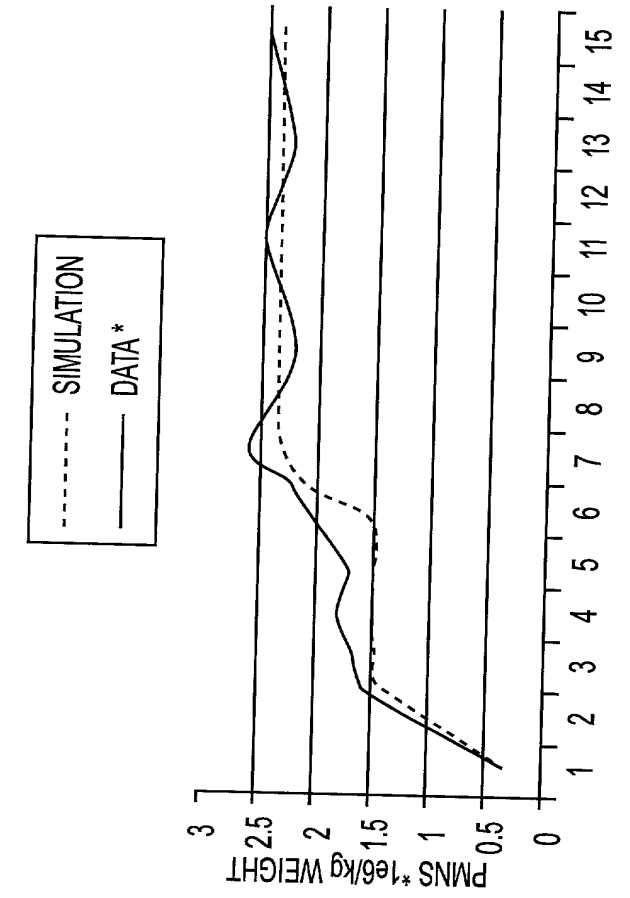

FIG. 12B

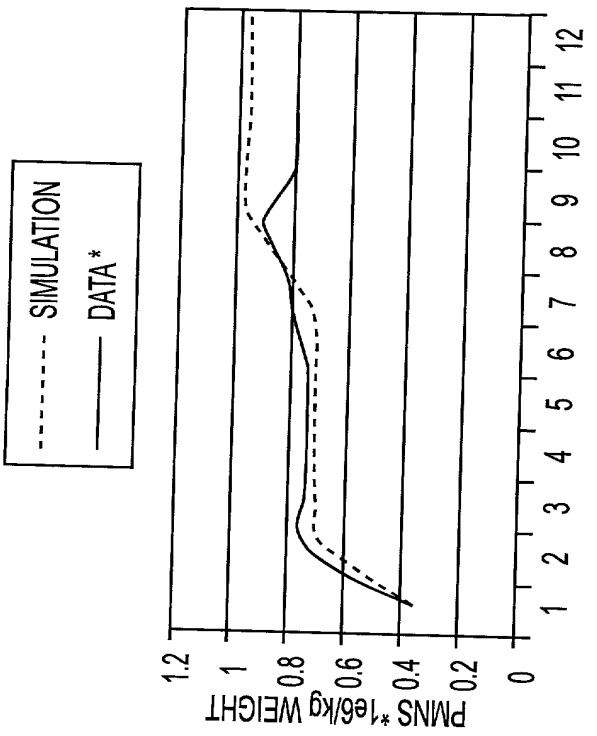

FIG. 12A

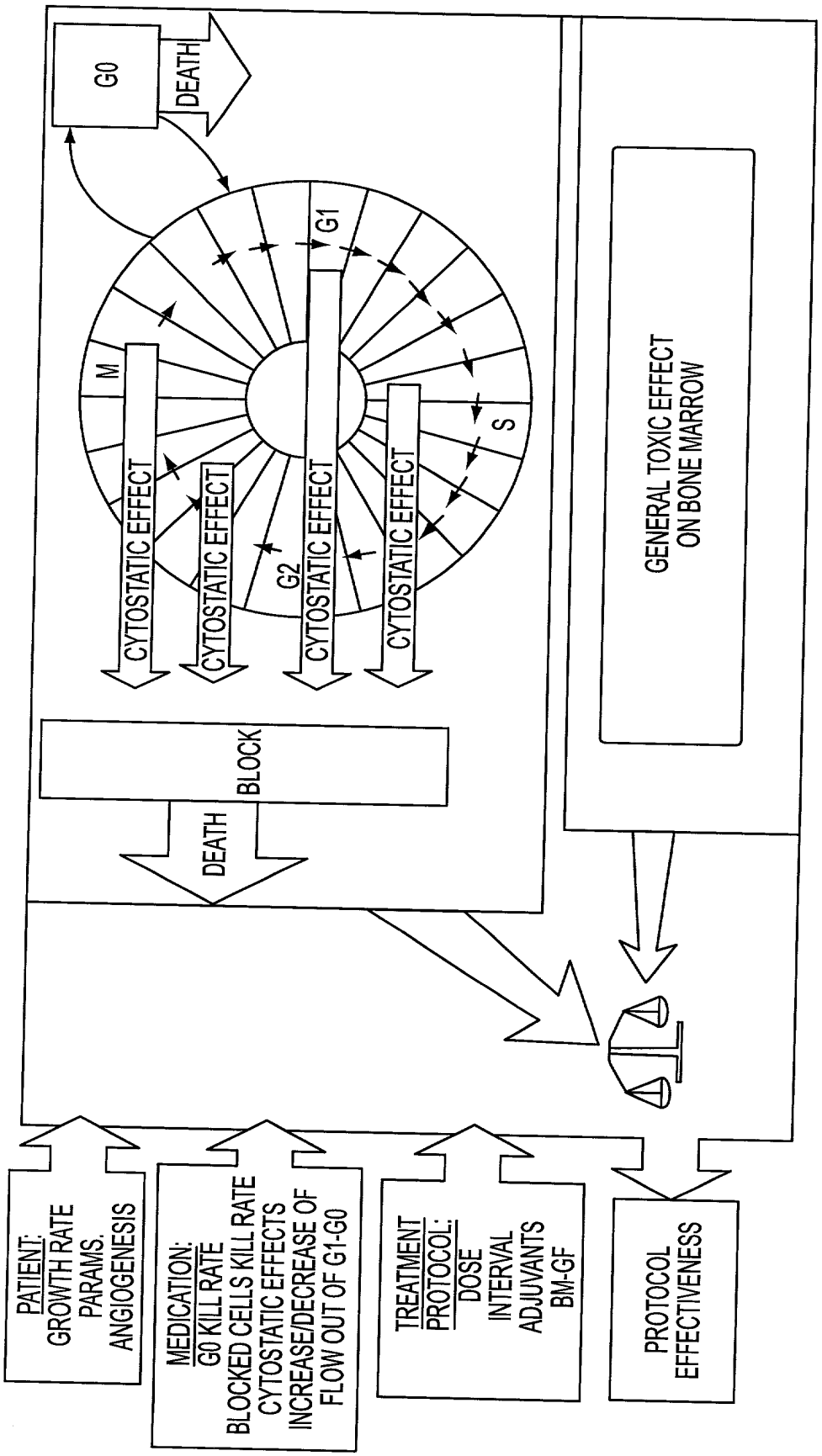
G0
DEATH
G1
M
S
G2
CYTOSTATIC EFFECT
CYTOSTATIC EFFECT
CYTOSTATIC EFFECT
CYTOSTATIC EFFECT
BLOCK
DEATH
GENERAL TOXIC EFFECT ON BONE MARROW
PATIENT: GROWTH RATE PARAMS. ANGIOGENESIS
MEDICATION: G0 KILL RATE BLOCKED CELLS KILL RATE CYTOSTATIC EFFECTS INCREASE/DECREASE OF FLOW OUT OF G1-G0
TREATMENT PROTOCOL: DOSE INTERVAL ADJUVANTS BM-GF
PROTOCOL EFFECTIVENESS

FIG. 13

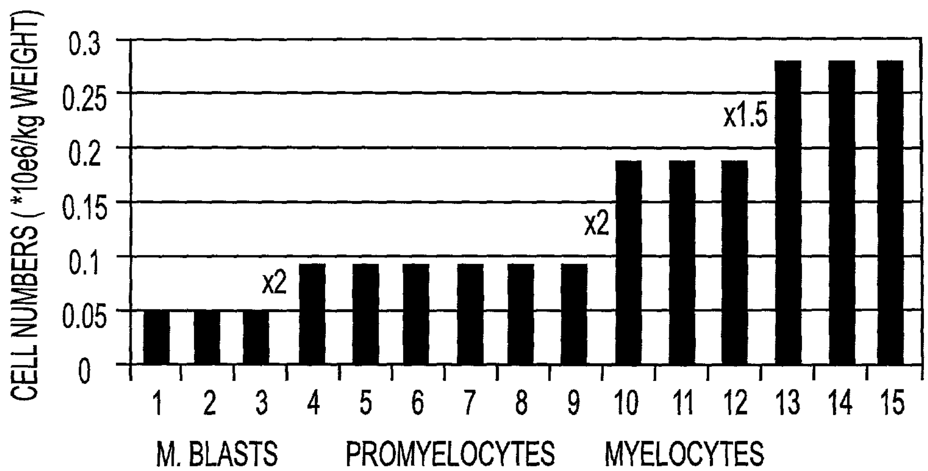

FIG. 14. SIMULATED MITOTIC COMPARTMENT AGE DISTRIBUTION AND AMPLIFICATION VALUES IN UNTREATED HUMANS. EACH BAR REPRESENTS A GROUPING OF 8 COHORTS OF ONE HOUR. AMPLIFICTION IS NOTED AT THE PLACE OF OCCURENCE.

FIG. 14

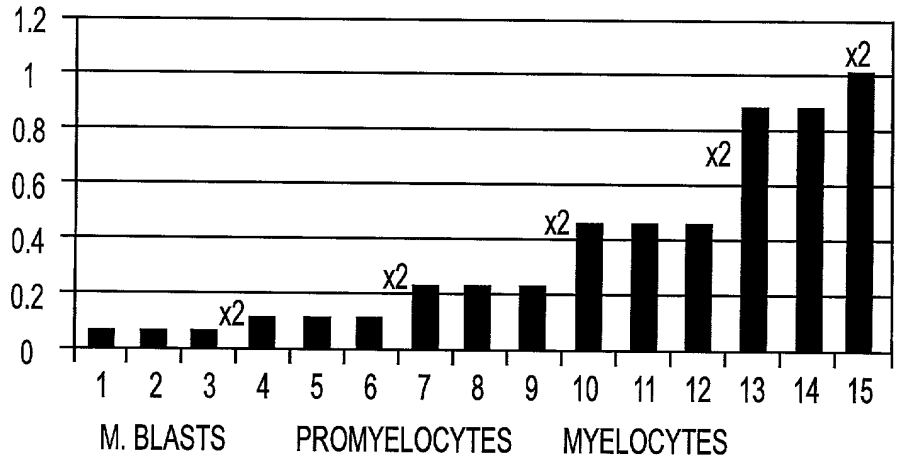

FIG. 15. SIMULATED MITOTIC COMPARTMENT AGE DISTRIBUTION AND AMPLIFICATION VALUES IN HUMANS TREATED WITH 300μg OF G-CSF AFTER 15 DAYS. EACH BAR REPRESENTS A GROUPING OF 8 COHORTS OF ONE HOUR. AMPLIFICATION IS NOTED AT THE PLACE OF OCCURRENCE. NOTE, THAT THE LAST HOURLY COHORT OF THE METAMYELOCYTES UNDERGOES MITOSIS, BUT ITS EFFECTS ARE DAMPENED IN THIS GRAPH DUE TO THE 8H GROUPING.

FIG. 15